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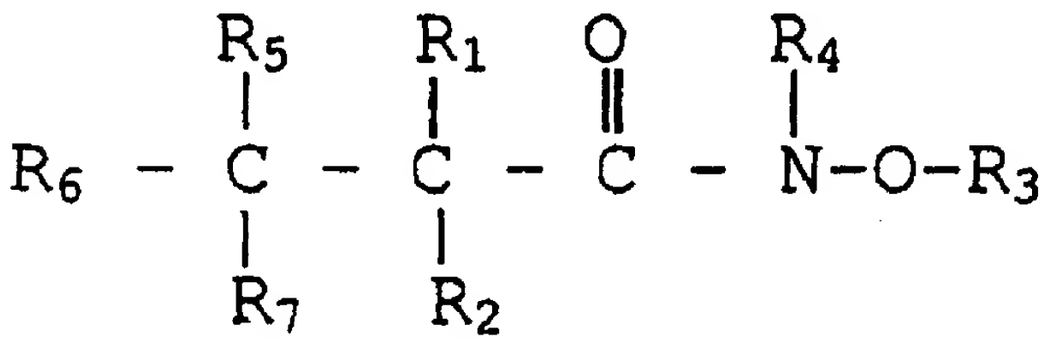
(54) Titre : UTILISATION DE 3-ISOXAZOLIDINONES ET D'HYDROXYLAMINOACIDES POUR LE TRAITEMENT D'INFECTIONS
(54) Title: USE OF 3-ISOXAZOLIDINONES AND HYDROXYLAMINE ACIDS FOR THE TREATMENT OF INFECTIONS



(I)

(57) Abrégé/Abstract:
The invention relates to medicaments containing at least one compound of the formula (I) and to their use for the therapeutic and prophylactic treatment of bacterial, fungal and parasitic infections in humans and animals.

Use of 3-isoxazolidinones and hydroxylamic acids for treatment of infections

The invention relates to the use of 3-isoxazolidinones and hydroxylamic acids as an active compound and their salts, esters and salts of the esters for therapeutic and prophylactic treatment of infections in humans and animals caused by bacteria, fungi and parasites.

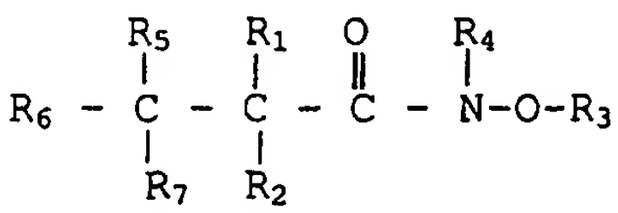
There is a great need to provide medicaments which have a potent activity against infections for enrichment of treatment of humans and animals.

The object of the present invention is therefore to provide a substance which can be employed on infections by bacteria, fungi and parasites in humans and animals and satisfies the abovementioned conditions.

US Patent Specification 4 405 357 discloses 3-isoxazolidinones and hydroxylamic acids as herbicides.

It has now been found, surprisingly, that 3-isoxazolidinones and hydroxylamic acids achieve the abovementioned object. This substance group shows an anti-infectious action against bacteria, fungi and mono- and multicellular parasites. According to the invention, monocellular parasites are to be understood as meaning protozoa.

The compounds contained according to the invention in the medicaments correspond to the general formula (I):



(I)

wherein R_3 is chosen from the group which consists of hydrogen, alkyl groups, alkoxy-(C_{0-26})-alkyl groups, C_{3-14}-cycloalkyl-(C_{0-26})-alkyl groups, cycloalkoxy-(C_{0-26})-alkyl groups, amino-(C_{0-26})-alkyl groups, silyl-(C_{0-26})-alkyl groups and thio-(C_{0-26})-alkyl groups, wherein each alkyl radical and each alkoxy radical can be branched or unbranched and each alkyl radical, each alkoxy radical and each cycloalkyl group can be saturated or unsaturated with one or more double or triple bonds and substituted by hydroxyl, amino, halogen, oxo groups and alkoxy radicals and one or two carbon atoms of the cycloalkyl groups can be replaced by nitrogen, oxygen or sulfur atoms,

R_4 is chosen from the group which consists of hydrogen, alkyl radicals, acyl radicals and cycloalkyl-(C_{0-26})-alkyl groups, wherein each alkyl radical and each acyl radical can be

branched or unbranched and each alkyl radical, each acyl radical and each cycloalkyl group can be saturated or unsaturated with one or more double or triple bonds and substituted by hydroxyl, amino, halogen, oxo groups and alkoxy radicals and one or two carbon atoms of the cycloalkyl groups can be replaced by nitrogen, oxygen or sulfur atoms,

R_1 and R_2 are identical or different and are chosen from the group which consists of hydrogen, hydroxyl, halogen, amino radicals, alkyl radicals, alkoxy radicals and cycloalkyl-(C_{0-26})-alkyl groups, wherein each alkyl radical and each alkoxy radical can be branched or unbranched and each amino radical, alkyl radical, each alkoxy radical and each cycloalkyl group can be saturated or unsaturated with one or more double or triple bonds and substituted by hydroxyl, amino, halogen, oxo groups and alkoxy radicals and one or two carbon atoms of the cycloalkyl groups can be replaced by nitrogen, oxygen or sulfur atoms,

R_5, R_6 and R_7 are identical or different and are chosen from the group which consists of hydrogen, hydroxyl, halogen, alkyl groups, cycloalkyl-(C_{0-26})-alkyl groups, cycloalkoxy-(C_{0-26})-alkyl groups, alkoxy-(C_{0-26})-alkyl groups, amino groups and thio-(C_{0-26})-alkyl groups and acyl radicals, wherein each alkyl radical, each alkoxy radical and each acyl radical can be branched or unbranched and each alkyl radical, each alkoxy radical and each cycloalkyl group can be saturated or unsaturated with one or more double or triple bonds and substituted by hydroxyl, amino, halogen, oxo groups and alkoxy radicals and one or two carbon atoms of the cycloalkyl groups can be replaced by nitrogen, oxygen or sulfur atoms,
wherein R_5 alternatively can also form a ring with R_1,
and R_3 and R_7 can contain a carbon-oxygen single bond such that a ring structure is present.

The invention also provides the pharmaceutically acceptable salts, esters and salts of the esters.

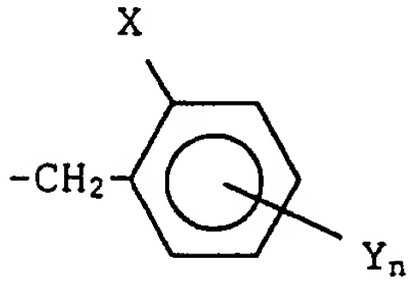
Preferably, R_1 and R_2 are identical or different and are chosen from the group which consists of substituted and unsubstituted alkyl groups, preferably C_1-C_4-alkyl groups.

Preferably, R_3 is chosen from the group which consists of hydrogen, substituted and unsubstituted alkyl groups, preferably C_1-C_4-alkyl groups, substituted and unsubstituted aromatic C_7-C_{14}-cycloalkyl groups, a pyranyl group, a t-butyldimethylsilyl group and

wherein R_8 is chosen from the group which ... [sic] of substituted and unsubstituted, preferably halogen-substituted, alkyl groups, substituted and unsubstituted cyloalkyl(C_{0-26})-

alkyl [sic] groups, substituted and unsubstituted amino groups, substituted and unsubstituted alkoxy groups, substituted and unsubstituted phenoxy groups, substituted and unsubstituted alkylthio groups, substituted and unsubstituted aromatic cycloalkylthio groups, preferably aromatic cycloalkylthio groups which are unsubstituted or substituted by halogen, methyl, methoxy, nitro, amino or CF_3 groups.

R_4 is preferably chosen from the group which consists of hydrogen, substituted and unsubstituted alkyl radicals, substituted and unsubstituted phenyl radicals and

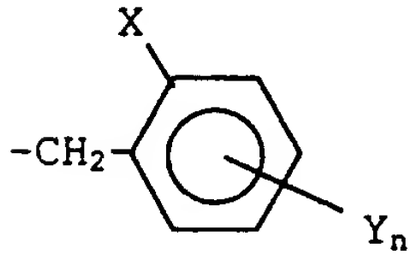


wherein X is chosen from the group which consists of hydrogen, halogen, C_{1-4}-alkyl radicals and phenyl radicals and Y is chosen from the group which consists of hydrogen, halogen, C_{1-4}-alkyl radicals, nitro radicals, methoxy radicals, methylenedioxy groups, wherein n is 0 or 1.

R_7 is preferably chosen from the group which consists of hydrogen and halogen, or
R_3 and R_7 contain a carbon-oxygen single bond such that a ring structure is present.

Particularly preferred compounds are those in which R_1 and R_2 independently of one another are chosen from the group which consists of methyl and ethyl,

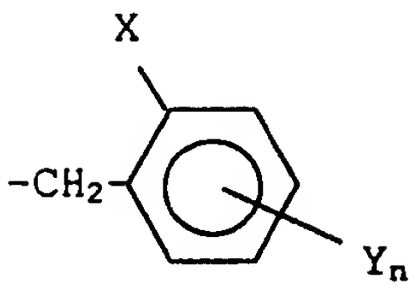
R_4 is



and

R_5 and R_6 independently are chosen from the group which consists of hydrogen, chlorine, bromine and methoxy groups.

Compounds which are preferred in particular are those in which R_4 is



wherein X is chosen from the group which consists of 2-chloro, 2-bromo, 2-fluoro, and Y is chosen from the group which consists of 4-chloro, 4-bromo, 4-fluoro, 5-fluoro and 4,5-methylenedioxy groups, wherein n is 0 or 1.

Compounds which are very particularly preferred are those in which R_1 and R_2 are methyl groups, R_3 and R_7 are hydrogen or contain a carbon-oxygen bond which form [sic] a ring structure.

Examples of preferred compounds are 3-chloro-N-(2-chlorophenyl)methyl-N-hydroxy-2,2-dimethylpropanamide, N-(2-chlorophenyl)methyl-N-hydroxy-2,2-Dimethylpropanamide, 3-chloro-N-hydroxy-N-phenyl-2,2-dimethylpropanamide, N-(2-bromophenyl)-methyl-3-chloro-N-hydroxy-2,2-dimethylpropanamide, 3-chloro-N-hydroxy-2,2-dimethyl-N-(2-methylphenyl)methylpropanamide, 3-chloro-N-hydroxy-2,2-N-trimethylpropanamide, 3-chloro-N-hydroxy-2,2-dimethyl-N-(phenylmethyl)-propanamide, 3-chloro-N-(2,4-dichlorophenylmethyl)-N-hydroxy-2,2-dimethylpropanamide, 3-chloro-N-(2-chlorophenyl)methyl-N-methoxy-2,2-dimethylpropan-amide, 3,3-dichloro-N-(2-chloropenyl)methyl-N-hydroxy-2,2-dimethylpropanamide [sic], 3-chloro-N-(2-fluorophenyl)methyl-N-hydroxy-2,2-dimethylpropanamide, 3-bromo-N-(2-chlorophenylmethyl-N-hydroxy-2,2-dimethylpropanamide, N-benzoyloxy-3-chloro-N-(2-chlorophenyl)methyl-2,2-dimethylpropanamide, N-acetoxy-3-chloro-N-(2-chlorophenyl)methyl-2,2-dimethylpropanamide, N-(chloroacetoxy)-3-chloro-N-(2-chlorophenyl)methyl-2,2-dimethylpropanamide, 2-(2-chlorophenyl)methyl-4,4-dimethyl-3-isoxazolidinone, 4,4-dimethyl-2-phenyl-3-isoxazolidinone, 2-(2-bromophenyl)methyl-4,4-dimethyl-3-isoxazolidinone, 4,4-dimethyl-2-(2-methyl-phenyl)methyl-3-isoxazolidinone, 2,4,-trimethyl-3-isoxazoli-dinone, 4,4-dimethyl-2-phenylmethyl-3-isoxazolidinone, 2-(2,4-dichlorophenyl)methyl-4,4-dimethyl-3-isoxazolidinone, 5-chloro-2-(2-chlorophenyl)methyl-4,4-dimethyl-3-isoxazolidinone, 2-(2-chlorophenyl)methyl-5-methoxy-4,4-dimethyl-3-isoxazoli-dinone, 2-(2-fluorophenyl)methyl-4,4-dimethyl-3-isoxazolidinone , N-[(2-chlorophenyl)methyl]-N,3-dihydroxy-2,2-dimethylpropanamide, 3-chloro-N-[(2-chlorophenyl)methyl]-2,2-dimethyl-N-(methylamino-carbonyloxy)propanamide, 3-chloro-N-[(2-chloro-phenyl)methyl]N-[(2-tetrahydropyranyl)oxyl-2,2-dimethyl-propanamide, 3-chloro-N-[(2-chlorophenyl)methyl]-2,2-dimethyl-N-[dimethyl(1,1-dimethyl-ethyl)silyloxypropanamide, 3-acetoxy-N-[(2-chlorophenoxy)-methyl]-N-hydroxy-2,2-dimethylpropanamide, 2,[(2-chloro-4-fluorophenyl)methyl]-4,4-dimethyl-3-isoxazolidinone,

2-[(2-chloro-5-fluorophenyl)methyl]-4,4-dimethyl-3-isoxazolidinone, 2-[(2,4,5-trichlorophenyl)methyl]-4,4-dimethyl-3-isoxazolidinone, 2-[(2-chloro-6-fluorophenyl)methyl]-4,4-dimethyl-3-isoxazoli-dinone, 2-[(2-chlorophenyl)methyl]-5-ethoxy-4,4-dimethyl-3-isoxazolidinone, 2-[(2-chlorophenyl)methyl]-4,4-dimethyl-5-phenylamino-3-isoxazolidinone, 2-[(2-chlorophenyl)methyl]-5-hydroxy-4,4-dimethyl-3-isoxazolidinone, 3-chloro-N-[(2-chloro-phenyl)methyl]-2,2-dimethyl-N-[(phenylamino)carbonyloxy]-propanamide, 3-chloro-N-[(2-chlorophenyl)methyl]-2,2-dimethyl-N-([(2-chlorophenyl)methyl]-2,2-dimethyl-N-phenoxycarbonyl-oxy)propanamide, 3-chloro-N-[(2-chlorophenyl)methyl]-N-ethoxy-carbonyloxy-2,2-dimethylpropanamide, N-benzoyloxy-3,3-dichloro-N-[(2-chlorophenyl)methyl]-2,2-dimethylpropanamide, N-(2-bromo-phenyl)methyl-3,3-dichloro-N-hydroxy-2,2-dimethyl)propanamide, 3-chloro-N-[(2-chlorophenyl)methyl]-N-(4-nitobenzoyloxy)-2,2-dimethylpropanamide [sic], 3-chloro-N-[2-chlorophenylm,ethyl)]-2,2-dimethyl-N-[(2-methylphenyl)carbonyloxy]propanamide, 3-chloro-N-dichloroacetoxy-N-[(2-chlorophenyl)methyl]-2,2-dimethylpropan-amide, 3-chloro-N-[2-chlorophenyl)methyl]-2,2-dimethyl-N-[(4-methylphenyl)sulfonyloxy]propanamide, 3-chloro-N-[2-chloro-phenyl)methyl]-2,2-dimethyl-N-[(1,1-dimethylethyl)carbonyl-oxy]propanamide, 3-chloro-N-[2-chlorophenyl)methyl]-2,2-dimethyl-N-(ethylthiocarbonyloxy)propanamide, 3-chloro-N-[(2,2,2-trichloroethoxy)carbonyloxy)-N-[(2-chlorophenyl)methyl]-2,3-dimethylpropanamide, 3-chloro-N-[(2-chlorophenyl)aminocarbonyl-oxy-N-[(2-chlorophenyl)methyl]-2,2-dimethylpropanamide, 3-chloro-N-[(4-chlorophenyl)aminocarbonyloxy-N-[(2-chlorophenyl)methyl]-2,2-dimethylpropanamide, 3-chloro-N-[2-chlorophenyl)methyl]-2,2-dimethyl-N-(phenylmethoxy)propanamide, 3-chloro-N-[(2,4-dichloro-phenyoxy)acetoxy)-N-[(2-chlorophenyl)methyl]-2,2-dimethyl-propanamide, , 3-chloro-N-[2-chlorophenyl)methyl]-2,2-dimethyl-N-[(3-trifluoromethyl)benzoyloxypropanamide, 3-chloro-N-[2-chloro-phenyl)methyl]-2,2-dimethyl-N-[(4-methylphenyl)aminocarbonyl-oxy)-propanamide, 3-chloro-N-[2-chlorophenyl)methyl]-N-[(3,4-chlorophenyl)aminocarbonyloxy]-2,2-dimethylpropanamide, 3-chloro-N-(3-chloro-2,2-dimethyl-1-oxo-propoxy)-N-[(2-chlorophenyl)-methyl]-2,2-dimethylpropanamide, 3-bromo-N-[(2-Bromophenyl)-methyl]-N-hydroxy-2,2-dimethylpropanamide, 3-chloro-N-[(2-chlorophenyl)methyl]-N-[(2-fluorophenyl)aminocarbonyloxy]-2,2-dimethylpropanamide,3-chloro-N-[(2-chlorophenyl)methyl]-N-[(4-methoxyphenyl)aminocarbonyloxy]-2,2-dimethylpropanamide, 3-chloro-N-[(2-chlorophenyl)methyl]-N-[(3-trifluoromethylphenyl)-aminocarbonyloxy]-2,2-dimethylpropanamide, 3-bromo-N-[(2-chlorophenyl)methyl]-N-(methylaminocarbonyloxy)-2,2-dimethyl-propanamide, 3-bromo-N-(2-chloroacetoxy)-N-[(2-chlorophenyl)-methyl]-2,2-dimethylpropanamide, 3-chloro-N-[2,5-dichloro-(formylamino)-benzoyl]oxy-N-[(2-chlorophenyl)methyl]-2,2-dimethylpropanamide, 3-bromo-N-[(2-bromophenyl)methyl]-N-chloroacetoxy-2,2-dimethylpropanamide, 3-bromo-N-[(2-bromophenyl)-methyl]-N-(methylcarbonyloxy)-2,2-dimethylpropanamide, 3-bromo-N-[(2-bromophenyl)methyl]-N-[(2-chlorophenyl)aminocarbonyloxy]-2,2-dimethylpropanamide, 2-[(2-chlorophenyl)methyl]-N-

hydroxy-2,2-dimethyl-3-methylthio-propanamide, 3-penylcarbonyloxy)-N-[(2-chlorophenyl)-methyl]-N-hydroxy-2,2-dimethylpropanamide [sic], 2-[(4-chlorophenyl)methyl]-4,4-dimethyl-3-isoxazolidinone, 2-[(3,4-dichlorophenyl)methyl]-4,4-dimethyl-3-isoxazolidinone, 2-[(chlorophenyl)methyl]-4,4-dimethyl-3-isoxazolidinon-5-yl acetate, 2-[(chlorophenyl)methyl]-4,4-dimethyl-3-isoxazoli-dinon-5-yl benzoate, 2-[(chlorophenyl)methyl]-4,4-dimethyl-3-isoxazolidinon-5-yl dichloroacetate, 2-[(chlorophenyl)methyl]-4,4-dimethyl-3-isoxazolidinon-5-yl phenylcarbamate, 2-[(chloro-phenyl)methyl]-4,4-dimethyl-3-isoxazolidinon-5-yl methyl-carbamate, 2-[(2-chloro-4-cyanophenyl)methyl]-4,4-dimethyl-3-isoxazolidinone, 2-[(2-chloro-5-methoxyphenyl)methyl]-4,4-dimethyl-3-isoxazolidinone, 2-[(2-chloro-4-methoxyphenyl)-methyl]-4,4-dimethyl-3-isoxazolidinone, 2-[(2,4-difluoro-phenyl)methyl]-4,4-dimethyl-3-isoxazolidinone, 2-[(4-bromo-2-chlorophenyl)methyl]-4,4-dimethyl-3-isoxazolidinone, 2-[(2-bromo-4-fluorophenyl)methyl]-4,4-dimethyl-3-isoxazolidinone, 2-[(6-chloro-1,3-benzdioxol-5-yl)methyl]-4,4-dimethyl-3-isoxazoli-dinone, 2-[(2-chlorophenyl)methyl]-4,4-dimethyl-5-phenoxy-3-isoxazolidinone, 2-[(2-chlorophenyl)methyl]-4,4-dimethyl-5-(1-methylethoxy)-3-isoxazolidinone, 2-[(2-chlorophenyl)methyl]-4,4-dimethyl-5-(phenylmethoxy)-3-isoxazolidinone, 2-[(2-bromo-phenyl)methyl]-5-chloro-4,4-dimethyl-3-isoxazolidinone, 2-[(2,5-dichlorophenyl)methyl]-4,4-dimethyl--3-isoxazolidinone, 2-[(2-chlorophenyl)methyl]-4,4-dimethyl-5-propoxy-3-isoxazolidinone, 2-[(2-chlorophenyl)methyl]-4,4-dimethyl-5-(2-propenyloxy)-3-isoxazolidinone, 2-[(2-chlorophenyl)methyl]-4,4-dimethyl-5-(2-propinyloxy)-3-isoxazolidinone, 2-[(2-chlorophenyl)methyl]-4,4-dimethyl-5-(2-methoxyethoxy)-3-isoxazolidinone, 2-[(4-fluoro-2-iodophenyl)methyl]-4,4-dimethyl-3-isoxazolidinone, 2-[(2-chloro-phenyl)methyl]-5-cyclopentoxy-4,4-dimethyl-3-isoxazolidinone, 2-[(2-chlorophenyl)methyl]-4,4-dimethyl-5-(4-nitophenoxy)-3-isoxazolidinone [sic], 2-[(2-chlorophenyl)methyl]-5-cyclopropyl-methoxy-4,4-dimethyl-3-isoxazolidinone, 2-[(2-bromophenyl-(methyl)]-4,4-dimethyl-5-(2-propinoxy)-3-isoxazolidinone, 2-[(2-chlorophenyl)methyl]-5-(3-butinoxy)-4,4-dimethyl-3-isoxazolidinone, 2-[(2-chlorophenyl)methyl]-5-(2-butinoxy)-4,4-dimethyl-3-isoxazolidinone, 2-[(2-chlorophenyl)methyl]-5-(3-butenoxy)-4,4-dimethyl-3-isoxazolidinone, 2-[(2-chlorophenyl)-methyl]-5-pentoxy-4,4-dimethyl-3-isoxazolidinone, 2-[(2-chloro-phenyl)methyl]-5-hexoxy-4,4-dimethyl-3-isoxazolidinone, 2-[(2-chlorophenyl)methyl]-5-(1-methylpropoxy)-4,4-dimethyl-3-isoxazolidinone, 2-[(2-chlorophenyl)methyl]-5-(3-methyl-3-butenoxy)-4,4-dimethyl-3-isoxazolidinone, 2-[(2-chlorophenyl)-methyl]-5-butoxy-4,4-dimethyl-3-isoxazolidinone, 2-[(2-chloro-phenyl)methyl]-4,4-dimethyl-3-isoxazolidinone.

Particulars of the above definitions and suitable examples of these are given below:

"Acyl" is a substituent which originates from an acid, such as from an organic carboxylic acid, carbonic acid, carbamic acid or the thio-acid or imide acid corresponding to the

individual above acids, or from an organic sulfonic acid, these acids in each case including aliphatic, aromatic and/or heterocyclic groups in the molecule, as well as carbamoyl or carbamimidoyl.

Suitable examples of these acyl groups are given below.

Acyl radicals originating from an aliphatic acid are designated aliphatic acyl groups, these including the following:
alkanoyl (e.g. formyl, acetyl, propionyl, butyryl, isobutyryl, valeryl, isovaleryl, pivaloyl etc.); alkenoyl (e.g. acryloyl, methacryloyl, crotonoyl etc.); alkylthioalkanoyl (e.g. methylthioacetyl, ethylthioacetyl etc.) alkanesulfonyl (e.g. mesyl, ethanesulfonyl, propanesulfonyl etc.); alkoxycarbonyl (e.g. methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, isopropoxycarbonyl, butoxycarbonyl, isobutoxycarbonyl etc.); alkylcarbamoyl (e.g. methylcarbamoyl etc.); (N-alkyl)-thiocarbamoyl (e.g. (N-methyl)-thiocarbamoyl etc.); alkylcarbamimidoyl (e.g. methylcarbamimidoyl etc.); oxalo; alkoxalyl (e.g. methoxalyl, ethoxalyl, propoxalyl etc.).

In the above examples of aliphatic acyl groups, the aliphatic hydrocarbon moiety, in particular the alkyl group or the alkane radical, can optionally contain one or more suitable substituents, such as amino, halogen (e.g. fluorine, chlorine, bromine etc.) hydroxyl, hydroxyimino, carboxyl, alkoxy (e.g. methoxy, ethoxy, propoxy etc.), alkoxycarbonyl, acylamino (e.g. benzyloxycarbonylamino etc.) acyloxy (e.g. acetoxy, benzoyloxy etc.) and the like; as preferred aliphatic acyl radicals with such substituents there may be mentioned e.g. alkanoyls substituted by amino, carboxyl, amino and carboxyl, halogen, acylamino or the like.

Those acyl radicals which originate from an acid with a substituted or unsubstituted aryl group are designated aromatic acyl radicals, it being possible for the aryl group to include phenyl, toluyl, xylyl, naphthyl and the like; suitable examples are given below:
aroyl (e.g. benzoyl, toluoyl, xyloyl, naphthoyl, phthaloyl etc.); aralkanoyl (e.g. phenylacetyl etc.); aralkenoyl (e.g. cinnamoyl etc.); aryloxyalkanoyl (e.g. phenoxyacetyl etc.); arylthioalkanoyl (e.g. phenylthioacetyl etc.); arylaminoalkanoyl (e.g. N-phenylglycyl, etc.); arenesulfonyl (e.g. benzenesulfonyl, tosyl or toluenesulfonyl, naphthalenesulfonyl etc.); aryloxycarbonyl (e.g. phenoxycarbonyl, naphthyl-oxycarbonyl etc.); aralkoxycarbonyl (e.g. benzyloxycarbonyl etc.); arylcarbamoyl (e.g. phenylcarbamoyl, naphthylcarbamoyl etc.); arylglyoxyloyl (e.g. phenylglyoxyloyl etc.).

In the above examples of aromatic acyl radicals, the aromatic hydrocarbon moiety (in particular the aryl radical) and/or the aliphatic hydrocarbon moiety (in particular the alkane radical) can optionally contain one or more suitable substituents, such as those which have

already been mentioned as suitable substituents for the alkyl group or the alkane radical. In particular, and as an example of preferred aromatic acyl radicals with particular substituents, aroyl substituted by halogen and hydroxyl or by halogen and acyloxy and aralkanoyl substituted by hydroxyl, hydroxyimino, dihalogenoalkanoyloxyimino are mentioned, as well as

arylthiocarbamoyl (e.g. phenylthiocarbamoyl etc.);
arylcarbamimidoyl (e.g. phenylcarbamimidoyl etc.).

A heterocyclic acyl radical is understood as meaning an acyl radical which originates from an acid with a heterocyclic group; this includes:

heterocyclic carbonyl in which the heterocyclic radical is an aromatic or aliphatic 5- to 6-membered heterocyclic radical with at least one heteroatom from the group consisting of nitrogen, oxygen and sulfur (e.g. thiophenyl, furoyl, pyrrolecarbonyl, nicotinoyl etc.);

heterocyclic alkanoyl in which the heterocyclic radical is 5- to 6-membered and contains at least one heteroatom from the group consisting of nitrogen, oxygen and sulfur (e.g. thiophenyl-acetyl, furylacetyl, imidazolylpropionyl, tetrazolylacetyl, 2-(2-amino-4-thiazolyl)-2-methoxyiminoacetyl etc.) and the like.

In the above examples of heterocyclic acyl radicals, the heterocyclic radical and/or the aliphatic hydrocarbon moiety can optionally contain one or more suitable substituents, such as the same as those which have already been mentioned as suitable substituents for alkyl and alkane groups.

"Alkyl", unless defined otherwise, is a straight- or branched-chain alkyl radical having up to 26 carbon atoms, such as methyl, ethyl, propyl, isopropyl, butyl, isobutyl, tert-butyl, pentyl, hexyl and the like. It can be substituted, e.g. by hydro-xyl, amino, halogen (e.g. fluorine, bromine, chlorine), oxo radicals and alkoxy radicals, such as methoxy, ethoxy radicals.

"Alkoxy radical", unless defined otherwise, is a straight- or branched-chain alkoxy radical having up to 26 carbon atoms, such as a methoxy, ethoxy radicals [sic] etc. It can be substituted, e.g. by hydroxyl, amino, halogen, oxo groups and alkoxy radicals, such as methoxy, ethoxy radicals.

"Alkoxy-(C_{0-26})-alkyl groups" are alkoxy radicals, which can also be bonded to the basic structure via an alkyl radical. The alkyl and alkoxy groups are as defined above.

"Cycloalkyl-(C_{0-26})-alkyl radicals" are cyclic compounds [sic] having 3 to 8 carbon atoms, unless defined otherwise, which are bonded to the basic structure directly or via an alkylene radical. The alkylene radical can be branched, unbranched and saturated or unsaturated with double bonds. Possible substituents of the cycloalkyl radical are, inter alia, alkoxy radicals, alkyl radicals, hydroxyl radicals, halogen radicals, amino radicals, oxo radicals. The cycloalkyl groups can also be aromatic with the corresponding number of double bonds, i.e. aryl-(C_{0-26})-alkyl radicals (e.g. phenyl, pyridyl, naphthyl etc.). The aromatic cyclic compounds in particular can furthermore contain substituents, such as nitro groups and CF_3 and phenyl radicals.

"Cycloalkoxy-(C_{0-26})-alkyl groups" are cyclic compounds [sic] having 3 to 8 carbon atoms which are bonded to the basic structure via an oxygen directly or via an alkylene radical. The alkylene radical can be branched, unbranched and saturated or unsaturated with double bonds. Possible substituents of the cycloalkyl radical are, inter alia, alkoxy radicals (including alkylenedioxy radicals, such as methylenedioxy), alkyl radicals, hydroxyl radicals, halogen radicals, amino radicals, oxo radicals. The cycloalkyl groups can also be polycyclic radicals and aromatic with the corresponding number of double bonds (e.g. phenoxy, pyridoxy, naphthoxy etc.). The aromatic cyclic compounds in particular can furthermore contain substituents, such as nitro groups, CF_3 groups and phenyl radicals.

"Amino radicals" can be substituted, for example by the alkyl radicals or cycloalkyl-(C_{0-26})-alkyl radicals as defined above

"Amino-(C_{0-26})-alkyl groups" are amino radicals, which can also be bonded to the basic structure via an alkyl radical. The alkyl and amino groups are as defined above.

"Silyl radicals" can be substituted, for example by the alkyl radicals or cycloalkyl-(C_{0-26})-alkyl radicals as defined above

"Silyl-(C_{0-26})-alkyl groups" are silyl radicals, which can also be bonded to the basic structure via an alkyl radical. The alkyl and silyl groups are as defined above.

"Thio-(C_{0-26})-alkyl groups" can be substituted, for example by the alkyl radicals or cycloalkyl-(C_{0-26})-alkyl radicals as defined above The (C_{0-26})-alkyl groups are straight- or branched-chain alkylene radicals, such as methylene, ethylene, propylene, isopropylene, butylene, isobutylene, tert-butylene, pentylene, hexylene and the like. They can contain double or triple bonds and can be substituted, e.g. by hydroxyl, amino, halogen (e.g. fluorine, bromine, chlorine), oxo radicals and alkoxy radicals, such as methoxy, ethoxy radicals.

The compounds of the formula (I) according to the invention allow, for example for groups R_1 to R_7 which contain double bonds or are chiral, the occurrence of steric isomers. The use according to the invention of the compounds includes all the steric isomers both as pure substances and in the form of their mixtures.

The compounds are suitable in particular for therapeutic and prophylactic treatment of infections in humans and animals caused by bacteria, mono- and multicellular parasites and fungi.

The compounds are active against monocellular parasites (protozoa), in particular against pathogens of malaria and sleeping sickness as well as Chagas's disease, toxoplasmosis, amoebic dysentery, leishmaniases, trichomoniasis, pneumocystosis, balantidiasis, cryptosporidiosis, sarcocystosis, acanthamoebiasis, naeglerosis, coccidiosis, giardiasis and lambliasis.

They are therefore particularly suitable as malaria prophylaxis and as prophylaxis of sleeping sickness as well as Chagas's disease, toxoplasmosis, amoebic dysentery, leishmaniases, trichomoniasis, pneumocystosis, balantidiasis, cryptosporidiosis, sarcocystosis, acanthamoebiasis, naeglerosis, coccidiosis, giardiasis and lambliasis.

The active compounds according to the invention can be employed in particular against the following bacteria:
bacteria of the family Propionibacteriaceae, in particular of the genus Propionibacterium, in particular the species Propionibacterium acnes, bacteria of the family Actinomycetaceae, in particular of the genus Actinomyces, bacteria of the genus Corynebacterium, in particular the species Corynebacterium diphteriae and Corynebacterium pseudotuberculosis, bacteria of the family Mycobacteriaceae, of the genus Mycobacterium, in particular the species Mycobacterium leprae, Mycobacterium tuberculosis, Mycobacterium bovis and Mycobacterium avium, bacteria of the family Chlamydiaceae, in particular the species Chlamydia trachomatis and Chlamydia psittaci, bacteria of the genus Listeria, in particular the species Listeria monocytogenes, bacteria of the species Erysipelthrix rhusiopathiae, bacteria of the genus Clostridium, bacteria of the genus Yersinia, of the species Yersinia pestis, Yersinia pseudotuberculosis, Yersinia enterocolitica and Yersinia ruckeri, bacteria of the family Mycoplasmataceae, of the genera Mycoplasma and Ureaplasma, in particular the species Mycoplasma pneumoniae, bacteria of the genus Brucella, bacteria of the genus Bordetella, bacteria of the family Neisseriaceae, in particular of the genera Neisseria and Moraxella, in particular the species Neisseria meningitides, Neisseria gonorrhoeae and Moraxella bovis, bacteria of the family Vibrionaceae, in particular of the genera Vibrio, Aeromonas, Plesiomonas and Photobacterium, in particular the species Vibrio cholerae,

Vibrio anguillarum and Aeromonas salmonicidas, bacteria of the genus Campylobacter, in particular the species Campylobacter jejuni, Campylobacter coli and Campylobacter fetus, bacteria of the genus Helicobacter, in particular the species Helicobacter pylori, bacteria of the families Spirochaetaceae and of Leptospiraceae, in particular of the genera Treponema, Borrelia and Leptospira, in particular Borrelia burgdorferi, bacteria of the genus Actinobacillus, bacteria of the family Legionellaceae, of the genus Legionella, bacteria of the family Rickettsiaceae and family Bartonellaceae, bacteria of the genera Nocardia and Rhodococcus, bacteria of the genus Dermatophilus, bacteria of the family Pseudomonadaceae, in particular of the genera Pseudomonas and Xanthomonas, bacteria of the family Enterobacteriaceae, in particular of the genera Escherichia, Klebsiella, Proteus, Providencia, Salmonella, Serratia and Shigella, bacteria of the family Pasteurellaceae, in particular of the genus Haemophilus, bacteria of the family Micrococcaceae, in particular of the genera Micrococcus and Staphylococcus, bacteria of the family Streptococcaceae, in particular of the genera Streptococcus and Enterococcus and bacteria of the family Bacillaceae, in particular of the genera Bacillus and Clostridium.

The compounds and their derivatives are therefore suitable for treatment of diphtheria, acne vulgaris, listerioses, erysipelas in animals, gas gangrene in humans and in animals, para-anthrax in humans and animals, tuberculosis in humans and animals, leprosy, and further mycobacterioses in humans and animals, paratuberculosis in animals, plague, mesenterial lymphadenitis and pseudotuberculosis in humans and animals, cholera, legionnaires' disease, borreliosis in humans and animals, leptospiroses in humans and animals, syphilis, Campylobacter enteritis in humans and animals, Moraxella keratoconjunctivitis and serositis in animals, brucelloses in animals and humans, anthrax in humans and animals, actinomycoses in humans and animals, streptotrichoses, psittacosis/ornithosis in animals, Q-fever, erlichiosis.

Use is furthermore beneficial in Helicobacter eradication treatment of ulcers of the gastrointestinal tract.

Combinations with a further antibiotic can also be employed for treatment of the abovementioned diseases. Isoniazid, rifampicin, ethambutol, pyrazinamide, streptomycin, protionamide and dapsone for treatment of tuberculosis are particularly suitable for combination preparations with other anti-infectives.

The compounds according to the invention, and these include in general pharmaceutically tolerated salts, esters and a salt of such an ester, or compounds which, on administration, provide the compounds according to the invention as metabolites or degradation products, also called "prodrugs", can be formulated for administration in any suitable manner

analogously to known agents having an anti-infectious action (mixed with a non-toxic pharmaceutically acceptable carrier).

Pharmaceutically acceptable salts of the compounds include salts which the compounds of the formula (I) according to the invention form in their protonated form as ammonium salts of inorganic or organic acids, such as hydrochloric acid, sulfuric acid, citric acid, maleic acid, fumaric acid, tartaric acid, p-toluenesulfonic acid.

Salts which are also particularly suitable pharmaceutically are those such as the sodium salt, potassium salt, calcium salt, ammonium salt, ethanolamine salt, triethylamine salt, dicyclohexylamine salt and salts of an amino acid, such as the arginine salt, aspartic acid salt, glutamic acid salt.

The activity of the substances is determined in a test system. The system is based on measurement of the inhibition of the growth of bacteria, parasites or fungi in vitro. Test methods which are known to the expert are used in part for this purpose.

For example, the inhibition of the growth of malaria parasites in blood cultures is determined for determination of the antimalaria activity.

The determination of the antibacterial activity is based on measurement of the inhibition of bacterial growth on nutrient media and in liquid cultures.

The determination of the fungicidal activity is based on inhibition of the growth of fungi on nutrient media and in liquid cultures.

Some of the microorganisms which are to be investigated can be investigated only in animal models. The corresponding models are used here.

Substances which show an activity in the in vitro measurement system are investigated further in models in vivo. The antiparasitic, fungicidal or antibacterial activity is evaluated further in the corresponding animal model.

The pharmaceutically active agents can be formulated in the form of pharmaceutical formulations in dosage units. This means that the formulation exists in the form of individual parts, e.g. tablets, coated tablets, capsules, pills, suppositories and ampoules, the active compound content of which correspond [sic] to a fraction or a multiple of an individual dose. The dosage units can comprise e.g. 1, 2, 3 or 4 individual doses or 1/2, 1/3 or 1/4 of an individual dose. An individual dose preferably comprises the amount of active compound

which is administered in one administration and which usually corresponds to a whole, a half or a third or a quarter of a daily dose.

Non-toxic, inert pharmaceutically suitable carrier substances are to be understood as meaning solid, semi-solid or liquid diluents, fillers and formulation auxiliaries of all types.

Preferred pharmaceutical formulations which may be mentioned are tablets, coated tablets, capsules, pills, granules, suppositories, solutions, suspensions and emulsions, pastes, ointments, gels, creams, lotions, powders and sprays. Tablets, coated tablets, capsules, pills and granules can comprise the active compound or compounds in addition to conventional carrier substances, such as (a) fillers and extenders, e.g. starches, lactose, sucrose, glucose, mannitol and silica, (b) binders, e.g. carboxymethylcellulose, alginates, gelatine, polyvinylpyrrolidone, (c) humectants, e.g. glycerol, (d) disintegrating agents, e.g. agar-agar, calcium carbonate and sodium carbonate, (e) solution retardants, e.g. paraffin and (f) absorption accelerators, e.g. quaternary ammonium compounds, (g) wetting agents, e.g. cetyl alcohol, glycerol monostearate, (h) adsorbents, e.g. kaolin and bentonite, and (i) lubricants, e.g. talc, calcium stearate and magnesium stearate and solid polyethylene glycols or mixtures of the substances listed under (a) to (i).

The tablets, coated tablets, capsules, pills and granules can be provided with the conventional coatings and shells, which optionally comprise opacifying agents, and can also be of a composition such that they release the active compound or compounds only or preferentially in a certain part of the intestinal tract, optionally in a delayed manner, it being possible to use e.g. polymer substances and waxes as embedding compositions.

The active compound or compounds can optionally also be in microencapsulated form together with one or more of the abovementioned carrier substances.

Suppositories can comprise, in addition to the active compound or compounds, the conventional water-soluble or water-insoluble carrier substances, e.g. polyethylene glycols, fats, e.g. cacao fat, and higher esters (e.g. C_{14}-alcohol with C_{16}-fatty acid) or mixtures of these substances.

Ointments, pastes, creams and gels can comprise, in addition to the active compound or compounds, the conventional carrier substances, e.g. animal and vegetable fats, waxes, paraffins, starch, tragacanth, cellulose derivatives, polyethylene glycols, silicones, bentonites, silica, talc and zinc oxide or mixtures of these substances.

Powders and sprays can comprise, in addition to the active compound or compounds, the conventional carrier substances, e.g. lactose, talc, silica, aluminium hydroxide, calcium silicate and polyamide powder or mixtures of these substances. Sprays can additionally comprise the conventional propellants, e.g. chlorofluorohydrocarbons.

Solutions and emulsions can comprise, in addition to the active compound or compounds, the conventional carrier substances, such as solvents, solubilizing agents and emulsifiers, e.g. water, ethyl alcohol, isopropyl alcohol, ethyl carbonate, ethyl acetate, benzyl alcohol, benzyl benzoate, propylene glycol, 1,3-butylene glycol, dimethylformamide, oils, in particular cottonseed oil, groundnut oil, maize germ oil, olive oil, castor oil and sesame oil, glycerol, glycerol formal, tetrahydrofurfuryl alcohol, polyethylene glycols and fatty acid esters of sorbitan or mixtures of these substances.

For parenteral administration, the solutions and emulsions can also be in a form which is sterile and isotonic with blood.

Suspensions can comprise, in addition to the active compound or compounds, the conventional carrier substances, such as liquid diluents e.g. water, ethyl alcohol, propylene glycol, suspending agents, e.g. ethoxylated isostearyl alcohols, polyoxyethylene sorbitol and sorbitan esters, microcrystalline cellulose, aluminium metahydroxide, bentonite, agar-agar and tragacanth or mixtures of these substances.

The formulation forms mentioned can also comprise colouring agents, preservatives and odour- and flavour-improving additives, e.g. peppermint oil and eucalyptus oil and sweeteners, e.g. saccharin.

The active compounds of the formula (I) should preferably be present in the abovementioned pharmaceutical formulations in a concentration of about 0.1 to 99.5 wt.%, preferably about 0.5 to 95 wt.% of the total mixture.

The pharmaceutical formulations can also comprise further pharmaceutical active compounds in addition to the compounds of the formula (I).

The compounds can be used with the substances described hitherto with antibacterial, antiviral, antimycotic and antiparasitic properties. These include, in particular, compounds which have already been used or are still being used in the treatment. Substances which are particularly suitable for this are those which are also listed in the Red List or in Simon/Stille, Antibiotika-Therapie in Klinik und Praxis [Antibiotic Treatment in the Hospital and Practice], 9th edition 1998 Schattauer Verlag, or on the Internet at http:/www.customs.treas.gov/imp-

exp/rulings/harmoniz/hrm129. html [sic]. In particular, the derivatives can ... [sic] with penicillins, benzylpenicillin (penicillin G), phenoxypenicillins, isoxazolylpenicillins, aminopenicillins, ampicillin, amoxixillin [sic], bacampicillin, carboxypenicillin, ticarcillin, temocillin, acyalaminopenicillins [sic], azlocillin, mezlocillin, piperacillin, apalcillin, mecillinam, cephalosporins, cefazolin group, cefuroxime group, cefoxitin group, cefoxitin, cefotetan, cefmetazole, latamoxef, flomoxef, cefotaxime group, cefozidime [sic], ceftazidime group, ceftazidime, cefpirome, cefepime, other cephalosporins, cefsulodin, cefoperazone, oral cephalosporins of the cefalexin group, loracarbef, cefprozil, new oral cephalosporins with an extended spectrum, cefixime, cefpodoxime-proxetil, cefuroxime-axetil, cefetamet, cefotiam-hexetil, cefdinir, ceftibuten, other β-lactam antibiotics, carbapenem, imipenem /cilastatin, meropenem, biapenem, aztreonam, ß-lactamase inhibitors, clavulanic acid/amoxicillin, clavulanic acid/ticarcillin, sulbactam/ampicillin, tazobactam/piperacillin, tetracyclines, oxytetracycline, rolitetraxyxline [sic], doxycycline, minocycline, chloramphenicol, aminoglycosides, gentamicin, tobramycin, netilmicin, amikacin, spectinomyxin, makrolides, erythromycin, clarithromycin, roxithromycin, azithromycin, dirithromycin, spiramycin, josamycin, lincosamide, clindamycin, fusidic acid, glycopeptide antibiotics, vancomycin, tecoplanin [sic], pristinamycin derivatives, fosfomycin, antimicrobial folic acid antagonists, sulfonamides, co-trimoxazole, trimethoprim, other diaminopyrimidine-sulfonamide combinations, nitrofurans, nitrofurantoin, nitrofurazone, gyrase inhibitors (quinolones), norfloxacin, ciprofloxacin, ofloxacin, sparfloxacin, enoxacin, fleroxacin, pefloxacin, lomefloxacin, Bay Y3118, nitroimidazoles, antimycobacterial agents, isoniazid, rifampicin, rifabutin, ethambutol, pyrazinamide, streptomycin, capreomycin, prothionamide, terizidone, dapsone, clofazimine, local antibiotics, bacitracin, tyrothricin, polymyxins, neomycin, kanamycin, paromomycin, mupirocin, antiviral agent, acyclovir, ganciclovir, azidothymidine, didanosine, zalcitabine, thiacytidine, stavudine, ribavirin, idoxuridine, trifluridine, foscarnet, amantadine, interferons, tibol derivatives, proteinase inhibitors, antimycotics, polyene, amphothericin B, nystatin, natamycin, azoles, azoles for sepsis treatment, miconazole, ketoconazole, itraconazole, fluconazole, UK-109.496, azoles for local use, clotrimazole, econazole, isoconazole, oxiconazole, bifonazole, flucytosine, griseofulvin, ciclopiroxolamine, tolnaftate, naftifine, terbinafine, amorolfine, anthraquinones, betulinic acid, semianthraquinones, xanthones, naphthoquinones, aryamino [sic] alcohols, quinine, quinidines, mefloquine, halofantrine, chloroquine, amodiaquine, acridine, benzonaphthyridine, mepacrine, pyronaridine, dapsone, sulfonamides, sulfadoxine, sulfalene, trimethoprim, proguanil, chlorproguanil, diaminopyrimidines, pyrimethamine, primaquine, aminoquinolines, WR 238,605, tetracycline, doxycycline, clindamycin, norfloxacin, ciprofloxacin, ofloxacin, artemisinine, dihydroartemisinine, 10b artemether, arteether, atrtesunate [sic], atovaquone, suramin, melarsoprol, nifurtmox [sic], stibogluconate sodium, pentamidine, amphotericin B, metronidazole, clioquinol, mebendazole, niclosamide,

praziquantel, pyrantel, tiabendazole, diethylcarbamazine, ivermectin, bithionol, oxamniquine, metrifonate, piperazine, embonate.

The compounds according to the invention can furthermore be present in the pharmaceutical compositions in combination with sulfonamide, sulfadoxine, artemisinine, atovaquone, quinine, chloroquine, hydroxychloroquine, mefloquine, halofantrine, pyrimethamine, armesine, tetracyclines, doxycycline, proguanil, metronidazole, praziquantil, niclosamide, mebendazole, pyrantel, tiabendazole, diethylcarbazine [sic], piperazine, pyrivinum, metrifonate, oxamniquine, bithionol or suramin or several of these substances.

The abovementioned pharmaceutical formulations are prepared in the conventional manner by known methods, e.g. by mixing the active compound or compounds with the carrier substance or substances.

The formulations mentioned can be used on humans and animals either orally, rectally, parenterally (intravenously, intramuscularly, subcutaneously), intracisternally, intravaginally, intraperitoneally, locally (powder, ointment, drops) and for treatment of infections in hollow spaces, body cavities. Possible suitable formulations are injection solutions, solutions and suspensions for oral treatment, gels, infusion formulations, emulsions, ointments or drops. Ophthalmological and dermatological formulations, silver salts and other salts, ear drops, eye ointments, powders or solutions can be used for local treatment. In the case of animals, uptake can also be via the feed or drinking water in suitable formulations. Gels, powders, dusts, tablets, sustained release tablets, premixes, concentrates, granules, pellets, tablets, boli, capsules, aerosols, sprays, inhalates can furthermore be used on humans and animals. The compounds according to the invention can furthermore be incorporated into other carrier materials, such as, for example, plastics (chains of plastic for local treatment), collagen or bone cement.

In general, it has proved advantageous both in human and in veterinary medicine to administer the active compound or compounds of the formula (I) in total amounts of about 0.05 to about 600, preferably 0.5 to 200 mg/kg body weight every 24 hours, optionally in the form of several individual doses, to achieve the desired results. An individual dose preferably comprises the active compound or compounds in amounts of about 1 to about 200, in particular 1 to 60 mg/kg body weight. However, in may be necessary to deviate from the dosages mentioned, and in particular according to the nature and body weight of the patient to be treated, the nature and severity of the disease, the nature of the formulation and the administration of the medicament and the period or interval within which administration takes place. Thus in some cases it may be sufficient to manage with less than the abovementioned amount of active compound, while in other cases the abovementioned amount of active

compound must be exceeded. The expert can specify the particular required optimum dosage and mode of administration of the active compounds on the basis of his expert knowledge.

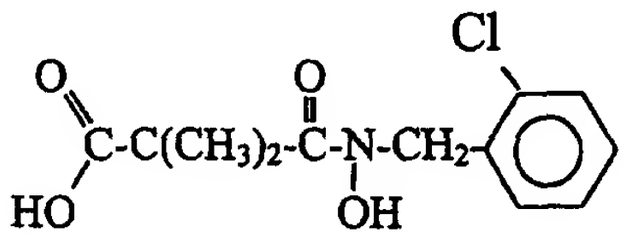
The compounds according to the invention can be administered to animals in the conventional concentrations and formulations together with the feed or with feed formulations or with the drinking water.

The preparation processes for the substances according to the invention are known to the expert e.g. from US-P-4 405 357.

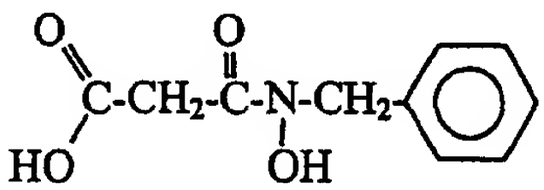
The activity of some compounds according to the invention is described below with the aid of examples:

The following substances are investigated:

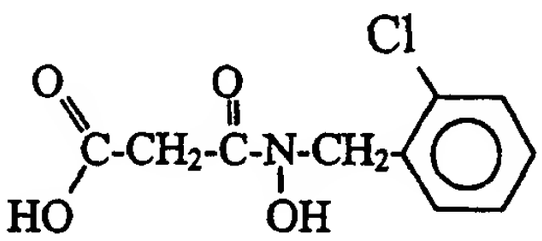
Substance 1:



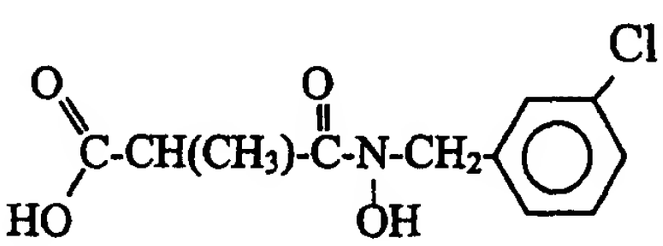
Substance 2:



Substance 3:



Substance 4:



Experiments show that the action of the compounds is based on inhibition of the 1-deoxy-D-xylulose 5-phosphate (DOXP) metabolic pathway, which can be detected in bacteria, parasites and fungi but not for humans. The following example accordingly shows the action of the compounds according to the invention on DOXP reductoisomerase.

Example 1

DOXP reductoisomerase of Escherichia coli was expressed as a recombinant protein in E.coli. The activity of the DOXP reductoisomerase was determined in a batch which comprised 100 mM Tris-HCl (pH = 7.5), 1 mM $MnCl_2$, 0.3 mM NADPH and 1 mM DOXP. The

oxidation of NADPH was measured here in a spectrophotometer at 365 nm. For carrying out the inhibition studies, the activity of the DOXP reductoisomerase in the presence of compounds 1 to 4 in various concentrations between 0.1 and 100 µmol l-1 was measured. The concentration at which the enzyme is inhibited to half the maximum extent (IC_{50}) was determined from the measurement values. The results, i.e. the IC50 values, are listed in the table.

Example 2

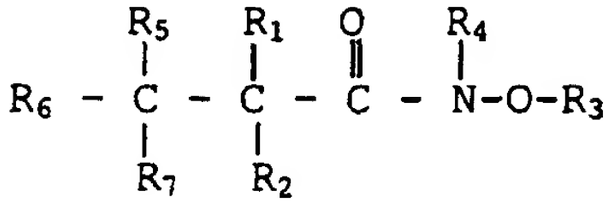
The antimalaria activity of substances 1 to 4 was determined on in vitro cultures of the malaria pathogen Plasmodium falciparum. The depressions of a 96-well microtitre plate were charged with in each case 200 µl of an asynchronous Plasmodium falciparum culture at a parasitaemia of 0.4% and haematocrit of 2%. A serial dilution series of the compounds in triple steps between concentrations of 100 to 0.14 µmol l^{-1} was then prepared. The plates were incubated at 37°C, 3% CO_2 and 5% O_2 over a period of 48 hours. 30 µl medium supplemented with 27 µCi ml^{-1} [^{3}H]-hypoxanthine were then added to each well. After incubation for 24 hours, the parasites were harvested by filtration on a glass fibre filter and the radioactivity which had been incorporated was measured. The inhibition of the parasite growth was measured as the percentage inhibition of the incorporation of tritium. The inhibition of the parasite growth was expressed as the percentage inhibition of the incorporation of tritium based on a comparison without the substance. The half-maximum inhibitory concentration (IC50) of the substance was determined by extrapolation of the values. The results, i.e. the IC50 values, are listed in the following table:

Table

Substance no.	IC50/(µM) (reductoisomerase)	IC50/(µM) (parasites)
1	20	28
2	37	32
3	24	33
4	40	48

Patent claims

1. Use of at least one compound of the formula (I)



(I)

R_3 is chosen from the group which consists of hydrogen, alkyl groups, alkoxy-(C_{0-26})-alkyl groups, C_{3-14}-cycloalkyl-(C_{0-26})-alkyl groups, cycloalkoxy-(C_{0-26})-alkyl groups, amino-(C_{0-26})-alkyl groups, silyl-(C_{0-26})-alkyl groups and thio-(C_{0-26})-alkyl groups, wherein each alkyl radical and each alkoxy radical can be branched or unbranched and each alkyl radical, each alkoxy radical and each cycloalkyl group can be saturated or unsaturated with one or more double or triple bonds and substituted by hydroxyl, amino, halogen, oxo groups and alkoxy radicals and one or two carbon atoms of the cycloalkyl groups can be replaced by nitrogen, oxygen or sulfur atoms,

R_4 is chosen from the group which consists of hydrogen, alkyl radicals, acyl radicals and cycloalkyl-(C_{0-26})-alkyl groups, wherein each alkyl radical and each acyl radical can be branched or unbranched and each alkyl radical, each acyl radical and each cycloalkyl group can be saturated or unsaturated with one or more double or triple bonds and substituted by hydroxyl, amino, halogen, oxo groups and alkoxy radicals and one or two carbon atoms of the cycloalkyl groups can be replaced by nitrogen, oxygen or sulfur atoms,

R_1 and R_2 are identical or different and are chosen from the group which consists of hydrogen, hydroxyl, halogen, substituted and unsubstituted amino radicals, substituted and unsubstituted alkyl radicals, substituted and unsubstituted alkoxy radicals and substituted and unsubstituted cycloalkyl-(C_{0-26})-alkyl groups, wherein each alkyl radical and each alkoxy radical can be branched or unbranched and each alkyl radical, each alkoxy radical and each cycloalkyl group can be saturated or unsaturated with one or more double or triple bonds and one or two carbon atoms of the cycloalkyl groups can be replaced by nitrogen, oxygen or sulfur atoms,

R_5, R_6 and R_7 are identical or different and are chosen from the group which consists of hydrogen, hydroxyl, halogen, substituted and unsubstituted C_1-C_{26}-alkyl groups, substituted and unsubstituted cycloalkyl-(C_{0-26})-alkyl groups, substituted and unsubstituted cycloalkoxy-(C_{0-26})-alkyl groups, substituted and unsubstituted cycloalkoxy-(C_{0-26})-alkyl groups [sic], substituted and unsubstituted amino groups,

unsubstituted thio-(C_{0-26})-alkyl groups and substituted or unsubstituted acyl radicals, wherein each alkyl radical, each alkoxy radical and each acyl radical can be branched or unbranched and each alkyl radical, each alkoxy radical and each cycloalkyl group can be saturated or unsaturated with one or more double or triple bonds and one or two carbon atoms of the cycloalkyl groups can be replaced by nitrogen, oxygen or sulfur atoms,
wherein R_5 alternatively can also form a ring with R_1,
and R_3 and R_7 can contain a carbon-oxygen single bond such that a ring structure is present,

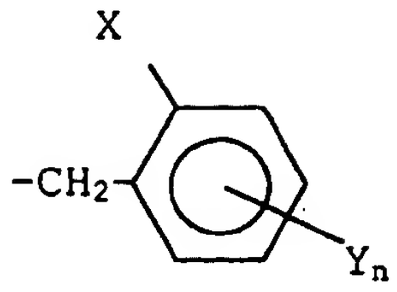
or their pharmaceutically acceptable salts, esters and salts of the esters, for prophylactic or therapeutic treatment of infections caused by bacteria, parasites or fungi.

2. Use according to claim 1, characterized in that R_1 and R_2 are identical or different and are chosen from the group which consists of substituted and unsubstituted alkyl groups, preferably C_1-C_4-alkyl groups.

3. Use according to one of the preceding claims, characterized in that R_3 is chosen from the group which consists of hydrogen, substituted and unsubstituted alkyl groups, preferably C_1-C_4-alkyl groups, substituted and unsubstituted aromatic C_7-C_{14}-cycloalkyl groups, a pyranyl group and a t-butyldimethylsilyl group and

in which R_8 is chosen from the group which consists of substituted and unsubstituted, preferably halogen-substituted, alkyl groups, substituted and unsubstituted cyloalkyl(C_{0-26})-alkyl [sic] groups, substituted and unsubstituted amino groups, substituted and unsubstituted alkoxy groups, substituted and unsubstituted phenoxy groups, substituted and unsubstituted alkylthio groups, substituted and unsubstituted aromatic cycloalkylthio groups, preferably aromatic cycloalkylthio groups which are unsubstituted or substituted by halogen, methyl, methoxy, nitro, amino or CF_3 groups.

4. Use according to one of the preceding claims, characterized in that R_4 is preferably chosen from the group which consists of hydrogen, substituted and unsubstituted alkyl radicals, substituted and unsubstituted phenyl radicals and

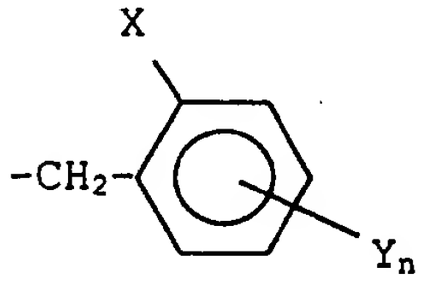


wherein X is chosen from the group which consists of hydrogen, halogen, C_{1-4}-alkyl radicals, phenyl radicals and Y is chosen from the group which consists of hydrogen, halogen, C_{1-4}-alkyl radicals, nitro radicals, methoxy radicals, methylenedioxy groups, wherein n is 0 or 1.

5. Use according to claim 4, characterized in that X is chosen from the group which consists of chlorine, bromine, fluorine, and Y is chosen from the group which consists of 4-chloro, 4-bromo, 4-fluoro, 5-fluoro and 4,5-methylenedioxy groups, wherein n is 0 or 1

6. Use according to one of the preceding claims, characterized in that R_7 is chosen from the group which consists of hydrogen and halogen or R_3 and R_7 contain a carbon-oxygen single bond such that a ring structure is present.

7. Use according to one of the preceding claims, characterized in that R_1 and R_2 independently of one another are chosen from the group which consists of methyl and ethyl,
R_4 is



R_5 and R_6 are chosen from the group which consists of hydrogen, chlorine, bromine and methoxy groups.

8. Use according to one of the preceding claims, characterized in that R_1 and R_2 are methyl groups, R_3 and R_7 are hydrogen or contain a carbon-oxygen bond which forms a ring structure.

9. Use according to claim 8, characterized in that it comprises as the active compound at least one substance from the group which consists of 3-chloro-N-(2-chlorophenyl)methyl-N-hydroxy-2,2-dimethylpropanamide, N-(2-chlorophenyl)methyl-

N-hydroxy-2,2-Dimethylpropanamide, 3-chloro-N-hydroxy-N-phenyl-2,2-dimethylpropanamide, N-(2-bromophenyl)-methyl-3-chloro-N-hydroxy-2,2-dimethylpropanamide, 3-chloro-N-hydroxy-2,2-dimethyl-N-(2-methylphenyl)methylpropanamide, 3-chloro-N-hydroxy-2,2-N-trimethylpropanamide, 3-chloro-N-hydroxy-2,2-dimethyl-N-(phenylmethyl)-propanamide, 3-chloro-N-(2,4-dichlorophenylmethyl)-N-hydroxy-2,2-dimethylpropanamide, 3-chloro-N-(2-chlorophenyl)methyl-N-methoxy-2,2-dimethylpropan-amide, 3,3-dichloro-N-(2-chloropenyl)methyl-N-hydroxy-2,2-dimethylpropanamide [sic], 3-chloro-N-(2-fluorophenyl)methyl-N-hydroxy-2,2-dimethylpropanamide, 3-bromo-N-(2-chlorophenylmethyl-N-hydroxy-2,2-dimethylpropanamide, N-benzoyloxy-3-chloro-N-(2-chlorophenyl)methyl-2,2-dimethylpropanamide, N-acetoxy-3-chloro-N-(2-chlorophenyl)methyl-2,2-dimethylpropan-amide, N-(chloroace-toxy)-3-chloro-N-(2-chlorophenyl)methyl-2,2-dimethylpropanamide, 2-(2-chlorophenyl)methyl-4,4-dimethyl-3-isoxazolidinone, 4,4-dimethyl-2-phenyl-3-isoxazolidinone, 2-(2-bromophenyl)methyl-4,4-dimethyl-3-isoxazolidinone, 4,4-dimethyl-2-(2-methyl-phenyl)methyl-3-isoxazolidinone, 2,4,-trimethyl-3-isoxazoli-dinone, 4,4-dimethyl-2-phenylmethyl-3-isoxazolidinone, 2-(2,4-dichloro-phenyl)methyl-4,4-dimethyl-3-isoxazolidinone, 5-chloro-2-(2-chlorophenyl)methyl-4,4-dimethyl-3-isoxazolidinone, 2-(2-chlorophenyl)methyl-5-methoxy-4,4-dimethyl-3-isoxazoli-dinone, 2-(2-fluorophenyl)methyl-4,4-dimethyl-3-isoxazolidi-none , N-[(2-chlorophenyl)methyl]-N,3-dihydroxy-2,2-dimethylpropanamide, 3-chloro-N-[(2-chlorophenyl)methyl]-2,2-dimethyl-N-(methylamino-carbonyloxy)propanamide, 3-chloro-N-[(2-chloro-phenyl)methyl]N-[(2-tetrahydropyranyl)oxyl-2,2-dimethyl-propanamide, 3-chloro-N-[(2-chlorophenyl)methyl]-2,2-dimethyl-N-[dimethyl(1,1-dimethyl-ethyl)silyloxypropanamide, 3-acetoxy-N-[(2-chlorophenoxy)-methyl]-N-hydroxy-2,2-dimethylpropanamide, 2,[(2-chloro-4-fluorophenyl)methyl]-4,4-dimethyl-3-isoxazolidinone, 2-[(2-chloro-5-fluorophenyl)methyl]-4,4-dimethyl-3-isoxazolidinone, 2-[(2,4,5-trichloro-phenyl)methyl]-4,4-dimethyl-3-isoxazolidinone, 2-[(2-chloro-6-fluorophenyl)methyl]-4,4-dimethyl-3-isoxazoli-dinone, 2-[(2-chlorophenyl)methyl]-5-ethoxy-4,4-dimethyl-3-isoxazoli-dinone, 2-[(2-chlorophenyl)methyl]-4,4-dimethyl-5-phenyl-amino-3-isoxazolidinone, 2-[(2-chlorophenyl)methyl]-5-hydroxy-4,4-dimethyl-3-isoxazolidinone, 3-chloro-N-[(2-chloro-phenyl)methyl]-2,2-dimethyl-N-[(phenylamino)carbonyloxy]-propanamide, 3-chloro-N-[(2-chlorophenyl)methyl]-2,2-dimethyl-N-([(2-chlorophenyl)methyl]-2,2-dimethyl-N-phenoxycarbonyl-oxy)propanamide, 3-chloro-N-[(2-chlorophenyl)methyl]-N-ethoxy-carbonyloxy-2,2-dimethylpropanamide, N-benzoyloxy-3,3-dichloro-N-[(2-chlorophenyl)methyl]-2,2-dimethylpropanamide, N-(2-bromo-phenyl)methyl-3,3-dichloro-N-hydroxy-2,2-dimethyl)propanamide, 3-chloro-N-[(2-chlorophenyl)methyl]-N-(4-nitobenzoyloxy)-2,2-dimethylpropanamide [sic], 3-chloro-N-[2-chlorophenylm,ethyl)]-2,2-dimethyl-N-

[(2-methylphenyl)carbonyloxy]propanamide, 3-chloro-N-dichloroacetoxy-N-[(2-chlorophenyl)methyl]-2,2-dimethylpropan-amide, 3-chloro-N-[2-chlorophenyl)methyl]-2,2-dimethyl-N-[(4-methylphenyl)sulfo-nyloxy]propanamide, 3-chloro-N-[2-chlorophenyl)methyl]-2,2-dimethyl-N-[(1,1-dimethylethyl)carbonyl-oxy]propanamide, 3-chloro-N-[2-chlorophenyl)methyl]-2,2-dimethyl-N-(ethylthio-carbonyloxy)propanamide, 3-chloro-N-[(2,2,2-trichloroethoxy)carbonyloxy)-N-[(2-chlorophenyl)methyl]-2,3-dimethylpropan-amide, 3-chloro-N-[(2-chlorophenyl)aminocarbonyl-oxy-N-[(2-chlorophenyl)methyl]-2,2-dimethylpropan-amide, 3-chloro-N-[(4-chlorophenyl)aminocarbonyloxy-N-[(2-chlorophenyl)methyl]-2,2-dimethylpropanamide, 3-chloro-N-[2-chlorophenyl)methyl]-2,2-dimethyl-N-(phenylmethoxy)propanamide, 3-chloro-N-[(2,4-dichloro-phenyoxy)acetoxy)-N-[(2-chlorophenyl)methyl]-2,2-dimethyl-propanamide, , 3-chloro-N-[2-chlorophenyl)methyl]-2,2-dimethyl-N-[(3-trifluoromethyl)benzoyloxypropanamide, 3-chloro-N-[2-chloro-phenyl)methyl]-2,2-dimethyl-N-[(4-methyl-phenyl)aminocarbonyl-oxy)-propanamide, 3-chloro-N-[2-chlorophenyl)methyl]-N-[(3,4-chlorophenyl)aminocarbonyloxy]-2,2-dimethylpropanamide, 3-chloro-N-(3-chloro-2,2-dimethyl-1-oxo-propoxy)-N-[(2-chlorophenyl)-methyl]-2,2-dimethylpropan-amide, 3-bromo-N-[(2-Bromophenyl)-methyl]-N-hydroxy-2,2-dimethylpropanamide, 3-chloro-N-[(2-chlorophenyl)methyl]-N-[(2-fluorophenyl)aminocarbonyloxy]-2,2-dimethylpropanamide,3-chloro-N-[(2-chlorophenyl)methyl]-N-[(4-methoxyphenyl)-aminocarbonyloxy]-2,2-dimethylpropanamide, 3-chloro-N-[(2-chlorophenyl)methyl]-N-[(3-trifluoromethylphenyl)-amino-carbonyloxy]-2,2-dimethylpropanamide, 3-bromo-N-[(2-chloro-phenyl)methyl]-N-(methylaminocarbonyloxy)-2,2-dimethyl-propanamide, 3-bromo-N-(2-chloroacetoxy)-N-[(2-chlorophenyl)-methyl]-2,2-dimethylpropanamide, 3-chloro-N-[2,5-dichloro-(formylamino)-benzoyl]oxy-N-[(2-chlorophenyl)methyl]-2,2-dimethylpropanamide, 3-bromo-N-[(2-bromophenyl)methyl]-N-chloroacetoxy-2,2-dimethylpropanamide, 3-bromo-N-[(2-bromophenyl)-methyl]-N-(methylcarbonyloxy)-2,2-dimethylpropan-amide, 3-bromo-N-[(2-bromophenyl)methyl]-N-[(2-chlorophenyl)-aminocarbonyloxy]-2,2-dimethylpropanamide, 2-[(2-chloro-phenyl)methyl]-N-hydroxy-2,2-dimethyl-3-methylthio-propanamide, 3-penylcarbonyloxy)-N-[(2-chlorophenyl)-methyl]-N-hydroxy-2,2-dimethylpropanamide [sic], 2-[(4-chlorophenyl)-methyl]-4,4-dimethyl-3-isoxazolidinone, 2-[(3,4-dichloro-phenyl)methyl]-4,4-dimethyl-3-isoxazolidinone, 2-[(chlorophenyl)methyl]-4,4-dimethyl-3-isoxazolidinon-5-yl acetate, 2-[(chlorophenyl)methyl]-4,4-dimethyl-3-isoxazoli-dinon-5-yl benzoate, 2-[(chlorophenyl)methyl]-4,4-dimethyl-3-isoxazo-lidinon-5-yl dichloroacetate, 2-[(chlorophenyl)methyl]-4,4-dimethyl-3-isoxazolidinon-5-yl phenylcarbamate, 2-[(chloro-phenyl)methyl]-4,4-dimethyl-3-isoxazolidinon-5-yl methyl-carbamate, 2-[(2-chloro-4-cyanophenyl)methyl]-4,4-dimethyl-3-isoxazolidinone, 2-[(2-chloro-5-methoxyphenyl)methyl]-4,4-dimethyl-3-isoxazolidinone, 2-[(2-chloro-4-

methoxyphenyl)-methyl]-4,4-dimethyl-3-isoxazolidinone, 2-[(2,4-difluoro-phenyl)methyl]-4,4-dimethyl-3-isoxazolidinone, 2-[(4-bromo-2-chlorophenyl)methyl]-4,4-dimethyl-3-isoxazolidinone, 2-[(2-bromo-4-fluorophenyl)methyl]-4,4-dimethyl-3-isoxazolidinone, 2-[(6-chloro-1,3-benzdioxol-5-yl)methyl]-4,4-dimethyl-3-isoxazolidinone, 2-[(2-chlorophenyl)methyl]-4,4-dimethyl-5-phenoxy-3-isoxazolidinone, 2-[(2-chlorophenyl)methyl]-4,4-dimethyl-5-(1-methylethoxy)-3-isoxazolidinone, 2-[(2-chlorophenyl)methyl]-4,4-dimethyl-5-(phenylmethoxy)-3-isoxazolidinone, 2-[(2-bromo-phenyl)methyl]-5-chloro-4,4-dimethyl-3-isoxazolidinone, 2-[(2,5-dichlorophenyl)methyl]-4,4-dimethyl--3-isoxazolidinone, 2-[(2-chlorophenyl)methyl]-4,4-dimethyl-5-propoxy-3-isoxazolidinone, 2-[(2-chlorophenyl)methyl]-4,4-dimethyl-5-(2-propenyloxy)-3-isoxazo-lidinone, 2-[(2-chlorophenyl)methyl]-4,4-dimethyl-5-(2-propinyloxy)-3-isoxazolidinone, 2-[(2-chlorophenyl)methyl]-4,4-dimethyl-5-(2-methoxyethoxy)-3-isoxazolidinone, 2-[(4-fluoro-2-iodophenyl)methyl]-4,4-dimethyl-3-isoxazolidinone, 2-[(2-chloro-phenyl)methyl]-5-cyclopentoxy-4,4-dimethyl-3-isoxazolidinone, 2-[(2-chlorophenyl)methyl]-4,4-dimethyl-5-(4-nitophenoxy)-3-isoxazolidinone [sic], 2-[(2-chlorophenyl)-methyl]-5-cyclopropyl-methoxy-4,4-dimethyl-3-isoxazoli-dinone, 2-[(2-bromophenyl-(methyl)]-4,4-dimethyl-5-(2-propinoxy)-3-isoxazolidinone, 2-[(2-chlorophenyl)methyl]-5-(3-butinoxy)-4,4-dimethyl-3-isoxazolidinone, 2-[(2-chloro-phenyl)methyl]-5-(2-butinoxy)-4,4-dimethyl-3-isoxazolidi-none, 2-[(2-chlorophenyl)methyl]-5-(3-butenoxy)-4,4-dimethyl-3-isoxazolidinone, 2-[(2-chlorophenyl)-methyl]-5-pentoxy-4,4-dimethyl-3-isoxazolidinone, 2-[(2-chloro-phenyl)methyl]-5-hexoxy-4,4-dimethyl-3-isoxazolidinone, 2-[(2-chlorophenyl)-methyl]-5-(1-methylpropoxy)-4,4-dimethyl-3-isoxazolidinone, 2-[(2-chlorophenyl)methyl]-5-(3-methyl-3-butenoxy)-4,4-dimethyl-3-isoxazolidinone, 2-[(2-chlorophenyl)-methyl]-5-butoxy-4,4-dimethyl-3-isoxazolidinone and 2-[(2-chloro-phenyl)methyl]-4,4-dimethyl-3-isoxazolidinone.

10. Use according to one of claims 1 to 9 for prevention and treatment of infections caused by monocellular parasites (protozoa), that is to say pathogens of malaria, sleeping sickness, Chagas's disease, toxoplasmosis, amoebic dysentery, leishmaniases, trichomoniasis, pneumocystosis, balantidiasis, cryptosporidiosis, sarcocystosis, acanthamoebiasis, naeglerosis, coccidiosis, giardiasis and lambliasis.

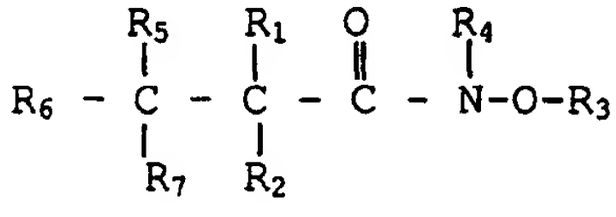
11. Use according to one of claims 1 to 9 for prevention and treatment of infections caused by bacteria which are chosen from the group which consists of bacteria of the family Propionibacteriaceae, in particular of the genus Propionibacterium, in particular the species Propionibacterium acnes, bacteria of the family Actinomycetaceae, in particular of the genus Actinomyces, bacteria of the genus Corynebacterium, in particular the species Corynebacterium diphteriae and Corynebacterium pseudotuberculosis, bacteria

of the family Mycobacteriaceae, of the genus Mycobacterium, in particular the species Mycobacterium leprae, Mycobacterium tuberculosis, Mycobacterium bovis and Mycobacterium avium, bacteria of the family Chlamydiaceae, in particular the species Chlamydia trachomatis and Chlamydia psittaci, bacteria of the genus Listeria, in particular the species Listeria monocytogenes, bacteria of the species Erysipelthrix rhusiopathiae, bacteria of the genus Clostridium, bacteria of the genus Yersinia, of the species Yersinia pestis, Yersinia pseudotuberculosis, Yersinia enterocolitica and Yersinia ruckeri, bacteria of the family Mycoplasmataceae, of the genera Mycoplasma and Ureaplasma, in particular the species Mycoplasma pneumoniae, bacteria of the genus Brucella, bacteria of the genus Bordetella, bacteria of the family Neisseriaceae, in particular of the genera Neisseria and Moraxella, in particular the species Neisseria meningitides, Neisseria gonorrhoeae and Moraxella bovis, bacteria of the family Vibrionaceae, in particular of the genera Vibrio, Aeromonas, Plesiomonas and Photobacterium, in particular the species Vibrio cholerae, Vibrio anguillarum and Aeromonas salmonicidas, bacteria of the genus Campylobacter, in particular the species Campylobacter jejuni, Campylobacter coli and Campylobacter fetus, bacteria of the genus Helicobacter, in particular the species Helicobacter pylori, bacteria of the families Spirochaetaceae and of Leptospiraceae, in particular of the genera Treponema, Borrelia and Leptospira, in particular Borrelia burgdorferi, bacteria of the genus Actinobacillus, bacteria of the family Legionellaceae, of the genus Legionella, bacteria of the family Rickettsiaceae and family Bartonellaceae, bacteria of the genera Nocardia and Rhodococcus, bacteria of the genus Dermatophilus, bacteria of the family Pseudomonadaceae, in particular of the genera Pseudomonas and Xanthomonas, bacteria of the family Enterobacteriaceae, in particular of the genera Escherichia, Klebsiella, Proteus, Providencia, Salmonella, Serratia and Shigella, bacteria of the family Pasteurellaceae, in particular of the genus Haemophilus, bacteria of the family Micrococcaceae, in particular of the genera Micrococcus and Staphylococcus, bacteria of the family Streptococcaceae, in particular of the genera Streptococcus and Enterococcus and bacteria of the family Bacillaceae, in particular of the genera Bacillus and Clostridium, and in Helicobacter eradication treatment of ulcers of the gastrointestinal tract.

12. Method for the treatment of infectious diseases caused by bacteria, fungi or parasites, in which a therapeutically active amount of a compound according to one of claims 1 to 11 is administered to a patient suffering from an infection caused by bacteria, fungi or parasites.

Abstract

The invention relates to medicaments with a content of at least one compound of the general formula (I)



(I)

and their use for therapeutic and prophylactic treatment of infections in humans and animals caused by bacteria, fungi and parasites.